

Unraveling the Intricacies of Host-Pathogen Interplay: Insights into SARS-CoV-2 and Beyond

Summer BIOCEV (MINI) SYMPOSIUM

The complexity and dynamic nature of the relationship between hosts and pathogens are overwhelming and require scientists across multiple disciplines to collaborate. This mini-symposium aims to deliver the newest insights into the methodologies, intricate mechanisms, molecular interactions, and immune responses involved in host-pathogen interactions presented by Czech and Japanese experts. We wish to inspire collaborations, knowledge transfer, and future research directions beyond the immediate context of the still ongoing pandemic.

Thursday, June 23, 2023

BIOCEV, Průmyslová 595, Vestec 252 50 – Czech Republic

Main Conference Hall

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Live stream will be available at: <https://live.biocev.org/stream>

Kei Sato, Ph.D.

Evolution of SARS-CoV-2

Professor: Division of Systems Virology, Institute of Medical Science, The University of Tokyo, Japan / Founder: The Genotype to Phenotype Japan (G2P-Japan) Consortium

At the end of 2019, SARS-CoV-2, the causative agent of COVID-19, emerged in China. As of January 2023, SARS-CoV-2 is still ongoing pandemic: more than six hundred million cases of SARS-CoV-2 infection have been reported worldwide, with more than six million people dying of COVID-19. During the spreading worldwide, SARS-CoV-2 has been diversified, and these SARS-CoV-2 variants are considered to be the potential threats to the human society. To elucidate the virological characteristics of newly emerging SARS-CoV-2 variants in real-time, I have launched a consortium called “The Genotype to Phenotype Japan (G2P-Japan)” in January 2021. With the colleagues joining in G2P-Japan consortium, we have revealed the virological characteristics of SARS-CoV-2 variants such as Delta (Saito et al., Nature, 2022), Omicron BA.1 (Suzuki et al., Nature, 2022; Meng et al., Nature, 2022), BA.2 (Yamasoba et al., Cell, 2022), BA.5 (Kimura et al., Cell, 2022; Yamasoba et al., Lancet Infect Dis, 2022), BA.2.75 (Saito et al., Cell Host Microbe, 2022), BQ.1.1 (Ito et al., Nat Commun, 2022), XBB (Tamura et al., Nat Commun, 2023; Uriu et al., Lancet Infect Dis, 2023; Yamasoba et al., Lancet Infect Dis, 2023) and so on. In this talk, I will briefly introduce the scientific activity of G2P-Japan consortium and would like to discuss the possibility for international collaboration to combat the outbreaks and pandemic that will happen in the future.

RNDr. Jiří Zahradník, Ph.D.

Probing Host-Pathogen Protein Interactions by yeast display

Laboratory of Protein Engineering, BIOCEV, First Faculty of Medicine, Charles University

Pathogens, particularly viruses, constantly adapt to outmaneuver their hosts. A significant part of this adaptation modulates protein-protein interactions between the host and the pathogen, an area where protein-engineering methodologies can substantially contribute. Among them, yeast display has emerged as a powerful tool for probing such changes.

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In my talk, I will explain and explore applications of enhanced yeast display to SARS-CoV-2 Receptor Binding Domain (RBD) - ACE2 interaction where multiple parallel solutions for the same interaction exist, supporting the same binding affinity yet providing enough space for immune escape.

Mgr. et Mgr. Evžen Bouřa, Ph.D.

RNA cap methylation in poxviruses and coronavirus – differences and similarities

Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences

RNA methyltransferases (MTases) are responsible for synthesizing the 5' RNA cap, which plays a crucial role in RNA stability and efficient translation (1). Over the past two years, both our research team and others have developed numerous inhibitors targeting coronaviral MTases (2-5). Through our efforts, we have successfully determined the crystal structures of these inhibitors bound to the coronaviral nsp14 and nsp16/nsp10 MTases (6, 7). Additionally, we recently elucidated the crystal structure of the monkeypox virus MTase VP39, in complex with the broad-spectrum MTase inhibitor sinefungin and several other inhibitors. These structural studies have unveiled notable distinctions between coronaviral and poxviral MTases, while also highlighting the potential for targeting these enzymes with the same or closely related compounds. This research was funded by the project the National Institute Virology and Bacteriology (Programme EXCELES, Project No. LX22NPO5103) - Funded by the European Union - Next Generation EU.

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Akatsuki Saito, D.V.M., Ph.D.

Host ZCCHC3 blocks HIV-1 infection and production by a dual mechanism

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Cells prevent viral infection and proliferation by expressing various restriction factors and sensors that activate the innate immune system. While anti-HIV-1 host restriction factors have been identified, some of them are antagonised by viral proteins. This has severely hindered their development in anti-HIV-1 therapy.

Here, we describe CCHC-type zinc-finger-containing protein 3 (ZCCHC3) as a novel anti-HIV-1 factor that is not antagonised by viral proteins. ZCCHC3 suppresses production of HIV-1 and other retroviruses. We show that ZCCHC3 acts by binding to Gag nucleocapsid protein via zinc-finger motifs. This prevents interaction between the Gag nucleocapsid protein and viral genome and results in production of genome-deficient virions. ZCCHC3 also binds to the long terminal repeat on the viral genome via the middle folded domain, sequestering the viral genome to P-bodies, which leads to decreased viral infectivity. Such a dual antiviral mechanism is distinct from that of any other known host restriction factors. Therefore, ZCCHC3 is a novel potential target in anti-HIV-1 therapy.

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Terumasa Ikeda, Ph.D.

APOBEC3 degradation is the primary function of HIV-1 Vif determining virion infectivity in the myeloid cell line THP-1

Division of Molecular Virology and Genetics, Joint Research Center for Human Retrovirus Infection, Kumamoto University, Kumamoto, Japan

HIV-1 must overcome multiple innate antiviral mechanisms to replicate in CD4⁺ T lymphocytes and macrophages. Previous studies have demonstrated that the APOBEC3 (A3) family of proteins (at least A3D, A3F, A3G, and stable A3H haplotypes) contribute to HIV-1 restriction in CD4⁺ T lymphocytes. Virus-encoded virion infectivity factor (Vif) counteracts this antiviral activity by degrading A3 enzymes allowing HIV-1 replication in infected cells. In addition to A3 proteins, Vif also targets other cellular proteins in CD4⁺ T lymphocytes, including PPP2R5 proteins. However, whether Vif primarily degrades only A3 proteins during viral replication is currently unknown. Herein, we describe the development and characterization of A3F-, A3F/A3G-, and A3A-to-A3G-null THP-1 cells. In comparison to Vif-proficient HIV-1, Vif-deficient viruses have substantially reduced infectivity in parental and A3F-null THP-1 cells, and a more modest decrease in infectivity in A3F/A3G-null cells. Remarkably, disruption of A3A–A3G protein expression completely restores the infectivity of Vif-deficient viruses in THP-1 cells. These results indicate that the primary function of Vif during HIV-1 infection in THP-1 cells is the targeting and degradation of A3 enzymes.

Prof. RNDr. Ivan Hirsch, CSc.

Hepatitis B virus: a stealth virus and the innate immunity

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Chronic hepatitis B virus (HBV) infection is a major health burden worldwide for which there is still no effective curative treatment. Early after infection, HBV replicates nearly uncontrolled within the infected liver, resulting in a majority of hepatocytes becoming infected. Immune activation and liver injury are negligible during this stage of infection. However, once the immune system recognizes HBV infection, which sometimes occurs only years after infection, a strong CD8 T cell response results in viral suppression accompanied by marked liver injury. HBV has been called a “stealth virus,” and the study of the impact of HBV on signaling pathways in the hepatocytes, and HBV interaction with non-parenchymal liver cells is important to understand viral pathogenesis. We investigate the interaction of the innate immunity with HBV-infected hepatocytes during the early steps of infection. We are also focused on the study of inhibitory mechanisms by which extracellular vesicles in the microenvironment of HBV-infected hepatocytes suppress activity of non-parenchymal innate immune cells. We try to understand sensing of viral infection and evasion of the innate immunity which is important for the development of antiviral therapies for cure.

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